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REVIEW ARTICLE

Incidental findings found in “healthy” volunteers during imaging performed for research: current legal and ethical implications

¹T C BOOTH, MA, MRCP, FRCR, ²A JACKSON, PhD, FRCR, FRCP, ³J M WARDLAW, MD, FRCR, FRCP, ⁴S A TAYLOR, MD, MRCP, FRCR and ⁵A D WALDMAN, PhD, MRCP, FRCR

¹Royal Free Hospital NHS Trust, Department of Radiology, Pond Street, London, UK, ²Wolfson Molecular Imaging Centre, University of Manchester, Manchester, UK, ³SFC Brain Imaging Research Centre, SINAPSE Collaboration, Division of Clinical Neurosciences, Western General Hospital, University of Edinburgh, Edinburgh, UK, ⁴Department of Medical Imaging, University of London, London, UK, and ⁵Department of Imaging, Imperial College Healthcare NHS Trust and Imperial College, London, UK

ABSTRACT. Incidental findings found in “healthy” volunteers during research imaging are common and have important implications for study design and performance, particularly in the areas of informed consent, subjects’ rights, clinical image analysis and disclosure. In this study, we aimed to determine current practice and regulations concerning information that should be given to research subjects when obtaining consent, reporting of research images, who should be informed about any incidental findings and the method of disclosure. We reviewed all UK, European and international humanitarian, legal and ethical agencies’ guidance. We found that the guidance on what constitutes incidental pathology, how to recognise it and what to do about it is inconsistent between agencies, difficult to find and less complete in the UK than elsewhere. Where given, guidance states that volunteers should be informed during the consent process about how research images will be managed, whether a mechanism exists for identifying incidental findings, arrangements for their disclosure, the potential benefit or harm and therapeutic options. The effects of incidentally discovered pathology on the individual can be complex and far-reaching. Radiologist involvement in analysis of research images varies widely; many incidental findings might therefore go unrecognised. In conclusion, guidance on the management of research imaging is inconsistent, limited and does not address the interests of volunteers. Improved standards to guide management of research images and incidental findings are urgently required.

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An incidental finding in a “healthy” volunteer participating in research imaging may be defined as “a finding that has potential health or reproductive importance which is discovered in the course of conducting research, but is beyond the aims of the study” [1]. A recent meta-analysis of 16 studies involving 19 559 participants found that the prevalence of incidental findings on brain MRI was 2.7% [2]. With body MRI, the prevalence is 12.8% [3], and with CT colonoscopy extra-colonic incidental findings require further investigation or medical or surgical intervention in 5–8% [4]. Therefore, incidental findings are common and have important implications for the process of informed consent, the need for clinical analysis of

images, mechanisms and pathways for notification of the subject and for the subject themselves.

Incidental findings could have serious implications for health, employment and medical and life insurance and for the volunteer’s state of mind. Furthermore, suspected abnormalities incorrectly identified by non-radiologically trained researchers could cause unnecessary alarm and upset to research volunteers. The analysis of research images and contingencies for dealing with incidental findings in the UK vary [3, 5, 6], although the limited systematic evidence concerning (and demonstrating) variation in practice is from overseas [7, 8]. This variation may reflect the lack of coherent, easily accessible guidelines and variations in existing guidance. In our experience as a group of researchers spread throughout the UK and imaging different organ systems, the involvement of radiologists in UK imaging research also varies widely, with much research being conducted remotely from radiology departments and without explicit mechanisms for expert image analysis.

Consequently, we have analysed UK, other European and other international legal and ethical resources to

Address correspondence to: T C Booth, Royal Free Hospital NHS Trust, Department of Radiology, Pond Street, London NW3 2QG, UK. E-mail: tombooth@doctors.org.uk

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determine whether there is any current guidance on the clinical and governance implications of elements of research imaging in normal subjects. Specifically we asked four questions:

- What information regarding the identification of incidental findings should be provided during the consent process?
- Should radiologists routinely report research images?
- To whom should incidental findings be disclosed?
- How should disclosure occur?

Methods and materials

We examined all available documents from the UK Department of Health (DoH) pertaining to the Research Governance Framework [9], the DoH's Governance arrangements for National Health Service (NHS) research ethics committees [10], and guidelines on research governance and practice produced by the General Medical Council (GMC) [11], the Medical Research Council (MRC) [12], the British Medical Association (BMA) [13] and the National Research Ethics Service (NRES) [14]. We also examined UK data protection law [15], European legislation [16, 17], international guidelines [18–20] and imaging research guidelines published in medical and legal journals (e.g. Appendix A [21, 22]).

The Westlaw database was used with expert assistance to search for relevant case law and legal journal articles relating to the Data Protection Act 1998 and Article Eight of the European Convention of Human Rights. The PubMed and MEDLINE databases were searched for articles published before April 2009 using the major topic MeSH term “Incidental Findings”. Articles on imaging in symptomatic volunteers were excluded.

We extracted all relevant statements on consent, disclosure of information to the subject and to medical practitioners, expert examination of images, and whether there was any organ system-specific or imaging modality-specific advice. We distinguished between guidance and regulations that apply in the UK and those that apply outside the UK.

Results

Consent

General principles

Consent by volunteers for participation in research is required ethically and, in most cases, legally under the Human Rights Act 1998 [13, 23], with additional conditions for children or mentally incapacitated volunteers [24–28]. Further guidance is available from organisations including the BMA and the GMC [13, 28]. The *Additional Protocol to the Convention on Human Rights and Biomedicine Concerning Biomedical Research*, agreed by the Council of Europe [17], requires written consent for participation in research and is legally binding under international law. The UK has not yet signed or ratified either the *Additional Protocol* or the *Convention* to which it relates; as and when

this occurs, there is likely to be a corresponding requirement that consent is in written format under UK domestic legislation. The Council for International Organizations of Medical Sciences (CIOMS), established by the World Health Organization (WHO) and United Nations Educational Scientific and Cultural Organization (UNESCO), requires informed consent of the prospective subject or, where an individual is not capable of giving informed consent, the permission of a legally authorised representative for all biomedical research involving humans [18]. These ethical guidelines are convergent with UK and European guidelines but are not, in themselves, legally binding.

Consent relating to incidental findings in the UK

The UK DoH recommends that, through ethics committee approval, arrangements are made to ensure that “relevant” information is provided to participants [9] and that “there are arrangements, if appropriate, for informing the research participant's general practitioner (GP), including procedures for seeking the participant's consent to do so” [10]. The meanings of “relevant” and “appropriate” in this context are open to interpretation, and will probably vary according to the requirements of individuals and the complexity of the procedures involved [11].

NRES includes the following explicit statements relevant to incidental findings in its published guidance on informed consent:

- “The subject must be adequately informed...of the possible disadvantages and risks of taking part...any risks, discomfort or inconvenience should be briefly outlined...the potential participant should be told what would happen if other conditions were discovered of which he or she was unaware...the published literature should be consulted and material presented to likely participant groups to assess its value...you should consider insurance issues and whether patients should be informed that their participation may affect insurance cover.
- Possible benefits should [also be outlined].
- You should explain if the participant's GP (or health care practitioner) needs to be notified of their participation, and seek consent. You should explain what information will be exchanged.
- [The participant should be told] how their confidentiality will be safeguarded during and after the study... You may wish to tell the participants how your procedures for handling, processing, storage and destruction of their data match the Caldicott principles and/or the Data Protection Act 1998...it must be clear if the data is to be retained for use in future studies and whether further [ethics committee] approval will be sought.”

The implications of the explicit instructions in the first point above are that mechanisms must be in place to identify and deal appropriately with incidental findings in a sensitive way, and that research subjects should be apprised of any insurance or other implications. Yet the low level of clinical and radiological involvement in most imaging research suggests that such mechanisms do not exist in most research imaging centres. We discuss the

final point concerning data handling in more detail in the section on data protection. An example of informed consent for neuroimaging research that addresses some of these NRES recommendations is presented in Appendix B [6].

Consent relating to incidental findings in Europe

The European *Additional Protocol to the Convention* requires that research participants are given comprehensible, documented information. Participants must be specifically informed of “any harm, and the available treatment” (but not explicitly regarding incidental findings) “and the arrangements made for responding to adverse events or the concerns of research participants”. This implies that information must be provided prior to the research examination on management pathways in the event of incidental findings.

Consent relating to incidental findings internationally

CIOMS guidelines require that, prior to obtaining consent, the investigator must provide information to the subject regarding incidental findings, including risks and benefits, that incidental findings will be disclosed, whether the investigator will be the subject's physician and “the extent of the investigator's responsibility to provide medical services to the participant” [20]. The unofficial United States (US) “Working Group on Incidental Findings in Brain Imaging Research” recommended that statistics about the incidence of unexpected findings and the proportion with potential clinical significance should be offered during the process of obtaining consent [29], which we have summarised in Appendix C. However, surveys have indicated that, in practice, adherence to both guidelines was variable. For example, consent for brain MRI research did not address processes for incidental findings in one US university, where 6.6% of “healthy” volunteers required clinical follow-up [30]. An example of the key points to be covered during the process of obtaining informed consent suggested by the US “Working Group on Incidental Findings in Brain Imaging Research” has since been published [22], which incorporates all the CIOMS guidelines except explicitly stating that incidental findings may have benefits.

Consent regarding future re-examination of imaging data

The evolution of new analysis methods and growing bioinformatic capability increases the possibility that imaging data will be re-analysed after the primary study has finished. The NRES states that it must be clear if the data is to be retained for use in future studies and whether further ethics committee approval will be sought. Some US authors take this a step further and recommend consent for future re-contact should an incidental finding be discovered in future re-analysis [1]. This latter recommendation is not yet a precedent and a recent study found that less than 5% of US institutions currently specify this [7].

Radiologist reporting of research images

A spectrum of models for reporting of research images by radiologists ranges from no radiology reporting at all, to “reactive radiology” where suspicious findings noticed by investigators are referred to a radiologist for an opinion, “proactive radiology” where all research images are reported and “very proactive radiology” where images additional to those required for the research may be acquired routinely to improve detection or characterisation of any incidental findings.

Advice and practice in the UK

The UK Medical Devices Agency (MDA) recommends that all volunteer MRI examinations are routinely reported by a radiologist [31]. There are no reliable data on how many UK institutions adhere to this guideline for MRI, and there are no equivalent guidelines on reporting of other imaging modalities used in research such as CT, ultrasound and positron emission tomography (PET). Indeed there are no reliable data from the UK on radiological involvement in research image examination.

Advice and practice in the US

Surveys in the US showed that neuroradiologist involvement in neuroimaging studies was an Institutional Review Board (IRB) requirement at 22% of research institutions [8]. Where it was not an IRB requirement, the majority of investigators surveyed said that, if they did notice something suspicious on imaging, they would consult with a radiologist for confirmation [32]. However, the clinically relevant images in such examinations (e.g. functional MRI) were often very limited, leading to the following typical statement on functional MRI consent forms: “On occasion the investigator may notice a finding on an MRI scan that seems abnormal. When this occurs, a neuroradiologist will be consulted as to whether the finding merits further investigation...Because the images collected in this study do not comprise a proper clinical MRI series, these images will not be made available for diagnostic purposes” [32]. Very few (<5%) institutions recommended checking whether an incidental finding was real or significant with a radiologist before its disclosure [7]. Moreover, the majority of the “Working Group on Incidental Findings in Brain Imaging Research” suggested that “reactive radiology” was necessary only if the research protocol included a means of disclosure [29].

Legal and ethical attitudes

Some legal authorities have stated that the reactive model ignores the duties owed to the subject in human research and may invite litigation [33]. For both medicolegal and ethical reasons, proactive involvement of specialist radiologists in research has been advocated, both for the detection of abnormalities and for their appropriate follow-up [34, 35]. This may already be more commonplace in some types of imaging research, for example radiologist analysis of research CT colonography for extra-colonic incidental findings [4]. Ethically, it has been argued that, as research subjects tacitly entrust a dimension of their health to the discretion of clinical investigators when they consent to participate in

research, “proactive radiology” should be an obligation [36, 37]. One ethical counter-argument is that the researchers’ duty is to research and not to promote health [38] and, therefore, incidental findings are of no consequence and can be ignored.

Volunteers’ attitudes

There is little information on what volunteers expect to be done about incidental findings on research images. Many volunteers may expect that expert examination of research images is routine [39]. In one of the few studies that has sought research volunteers’ opinions, the majority of the volunteers in neuroimaging research expected that their images would be examined and medical anomalies disclosed to them [40], regardless of what written information they were given during the consent process or whether the research took place in a medical or non-medical environment. At a SINAPSE Collaboration (Scottish Imaging Network, A Platform for Scientific Excellence) debate, all 70 attendants indicated that, if participating in a research study, they would wish to have their images examined by a radiologist, and any incidental finding disclosed to them and discussed with a responsible physician [41].

Do missed incidental findings cause harm?

The evidence base to support a “proactive” policy is limited. A review in 2004 found no documented adverse outcome due to a missed finding in the legal or medical literature [8]. It has been argued, therefore, that routinely reporting research images for incidental findings is not an ethical imperative [36]; however, this information is likely to be incomplete.

Practical considerations

The “reactive radiology” approach assumes that the task of identifying abnormal findings is simple, yet this may be a particularly difficult task for a researcher not trained in radiology [39]. Also, “proactive radiology” is limited as imaging protocols used in research are frequently not optimal for detection of incidental disease. For example, during functional MRI studies of the brain in cognitive neuroscience research, only limited structural images are usually acquired, and these are relatively insensitive to pathology. Similarly, research CT colonography often employs low-dose techniques, limiting evaluation of extra-colonic structures. An explanation of the diagnostic limitations of research imaging techniques may therefore be essential to the consent process [4]. Routine additional imaging — “very proactive radiology” — may increase sensitivity to incidental findings [39]. However, this model would increase cost and could be impractical, as in some situations a substantial number of additional sequences would be required. Nonetheless, research at the US National Institute of Health follows this “very proactive” model [42], which at least one US litigation lawyer argues should be standard practice [33].

It has been argued that it may be more appropriate to have a menu of practical options for screening incidental neuroimaging findings appropriate to different research settings [22], ranging from no examination for incidental findings through to a “very proactive” approach

depending on the circumstances. The US “Working Group on Incidental Findings in Brain Imaging Research” eventually concluded that strict regulations for handling incidental findings are not appropriate given the present state of knowledge [29]. Instead, the authors advocated clear informed consent and communication at disclosure, rather than a “one size fits all” radiological examination option. In general, radiological reporting of research images has considerable cost implications, which are beyond the scope of the present paper and vary with the healthcare and research funding models in different countries. However, at least some of these costs could be offset by discounts for research, for imaging volume or by written acknowledgment of the radiologist’s input. Full authorship on resultant publications may be appropriate where the radiologist is a full member of the research team [29, 30].

Disclosure

UK data protection legislation

The Data Protection Act 1998 [15] establishes the legal framework for protection of personal data, with explicit obligation to provide “data subjects” with information about who is handling their personal data and for what purposes. Volunteers must be informed if, for example, the GP will be told of any abnormal findings or if a copy of the imaging or a report is routinely added to the hospital clinical records. Incidental findings fall within the Act definition of “sensitive personal data”, and volunteers may need to give their explicit consent to the disclosure of an incidental finding to themselves. Although research exemptions exist, they are not relevant to incidental findings which support decisions relating to particular individuals [13]. For example, an exemption cannot be used to prevent the volunteer accessing any personal data that revealed incidental findings. The Act underpins MRC and GMC guidance [11, 43] and Research Governance Framework and NRES requirements that research data will be appropriately managed and can be disclosed only to authorised persons such as researchers, sponsors, regulatory authorities and auditors [9, 10, 13].

In the US, radiological research guidelines strongly recommend that a Certificate of Confidentiality is provided for research subjects involved in illegal behaviour (e.g. neuroimaging in cocaine users). The certificate is designed to allow investigators to refuse to disclose research data with private identifiable information to a civil or judicial authority, even when the data are requested under the authority of a subpoena [21]. No similar legally binding confidentiality agreement is available in the UK.

Consequences of disclosure to the volunteer

The balance between the risk and benefit of disclosing unexpected findings depends on the significance of imaging findings in diagnosis of asymptomatic disease and the impact of early intervention on outcome.

Early identification of an incidental finding might be of unequivocal benefit to the patient if the condition is treatable and early diagnosis improves outcome. For

example, renal cell carcinoma is not uncommon in a largely “healthy” population [44] and can be detected earlier with imaging than at symptomatic presentation [45–47] with significant improvement in prognosis [48, 49]. In Japan, a reduction in renal cell carcinoma mortality has been attributed to a rise in incidentally discovered lesions [50]. A similar argument applies to incidental abdominal aortic aneurysms larger than 5 cm [51]. Many incidental neuroimaging findings are, however, of indeterminate clinical significance [36], with poorly characterised natural history and unpredictable individual outcomes [52]; thus, treatment is of questionable benefit [39].

The adverse effects of disclosing incidental findings include anxiety, which may be considered “unnecessary” if the incidental finding is subsequently shown to have no clinical importance [1, 53]. Incidental findings can also adversely affect medical and life insurance and have implications for future employment. Harm may also result from further investigation of indeterminate or suspicious findings, including exposure to ionising radiation or more invasive procedures such as biopsy [54, 55] or unnecessary treatment. During follow-up of indeterminate extra-cardiac findings in a prospective cardiac CT study ($n=966$), each patient underwent additional diagnostic investigations with an estimated mean effective dose of 9.4 mSv; of these, 12% underwent invasive diagnostic procedures such as transthoracic biopsy or bronchoscopy [56]. Data from the Japanese atomic bomb survivors [57–59] and radiation workers in the nuclear industry [60, 61] show that ionised radiation doses as low as 5 mSv may increase the risk of cancer. With follow-up, none of the indeterminate findings became clinically significant. The authors concluded that such false-positive findings may lead to increased costs (mean US\$508 per patient with an indeterminate finding), increase patient morbidity, reduce patient quality of life and have no clear mortality benefit.

These problems are compounded by the rapid advances in the sensitivity of imaging technology, increasing the chances of discovering incidental findings whilst experience in interpretation of findings of these early pre-symptomatic pathologies remains limited [62].

When to disclose — ethical background

Advice on disclosure of incidental findings found on imaging is inconsistent and incomplete. The obligation to disclose research results to volunteers has been argued forcefully for genetic research results [63] and is increasingly suggested for other types of clinical research data [64]. Some ethicists argue that the principles of respect for persons, reciprocity, beneficence and justice oblige researchers to offer results to research participants [65]. Others argue that if the process of disclosure to volunteers is inadequate, disclosure may not be the ethical imperative. In genetic studies, researchers and participants have highlighted the constraints of embedded clinical services limited by funds [66], namely delays in receiving test results and researchers demonstrating insufficient clinical sensitivity towards subjects. If disclosure is considered an ethical imperative, then funding agencies must support satisfactory clinical services [65].

When to disclose — UK advice

The DoH requires that ethics committees ensure that there are “arrangements, if appropriate, for informing the research participant’s GP” [10]. However, this statement is ambiguous. “If appropriate” is not qualified and it is unclear whether the GP is informed merely that the participant has been involved in an imaging study or whether the GP is informed of all results including incidental findings. The NRES requires that processes for dealing with incidental findings are incorporated in the consent process, but does not mandate disclosure of incidental findings to volunteers. The MDA recommends disclosure when incidental findings are identified in all volunteers undergoing MRI, followed by appropriate onward clinical referral [31]. This recommendation is concordant with the wishes of 100% of a sample of potential volunteers [41]. There are no other explicit UK recommendations to disclose incidental findings to volunteers, except if the volunteer specifically requests disclosure. Here they would have a right, under section seven of the Data Protection Act, to have access to incidental findings.

When to disclose — European and US advice

The European *Additional Protocol to the Convention* (Article 27) states “If research gives rise to information of relevance to the current or future health or quality of life of research participants, this information must be offered to them” [17]. Disclosing only “relevant” incidental findings is a practical approach, as only a small percentage of findings are clinically relevant [32]. However, it is uncertain how to determine reliably what incidental finding is “relevant” for each research participant in the absence of symptomatology [66].

CIOMS recommend disclosure of “any finding that relates to their particular health status” [20]. In one US study, over 90% of neuroimaging volunteers wanted findings communicated to them [40]. However, some consider it unwise to communicate all but the most certain, clinically important, incidental findings (Appendix D) [1, 29, 67]. Indeed, in order to comply with US Federal regulations, researchers should minimise risks to participants, including the adverse effects of false-positives as described above [1].

Current practice reflects that both approaches of disclosing unexpected findings (all findings or “relevant” findings) are commonly used: in a US and European survey of CT colonography research programmes ($n = 12$), 58% reported all extra-colonic findings and 42% reported “relevant” extra-colonic findings [4].

When not to disclose

The *Additional Protocol to the Convention*, CIOMS and other international guidelines from groups including the “Working Group on Incidental Findings in Brain Imaging Research” recognise that the wishes of individuals not to be informed should be observed [16, 63, 68]. However, the World Medical Association, which represents approximately 80 national medical associations, and the GMC would not respect the refusal by an individual to receive incidental findings if “required for the protection of another person’s life” [11, 19]. An example would be finding a potentially epileptogenic

brain tumour in a bus driver who happened to be a research volunteer; even if this person did not wish their findings be disclosed to them, there is an ethical duty to do so.

How to disclose

In the UK, DoH and NRES regulations do not state how incidental findings should be communicated, but the implication from the DoH is that the participant’s GP should be involved [10, 13].

In Europe, the Appendix to the *Additional Protocol to the Convention* states that relevant incidental findings should be disclosed within a framework of healthcare or counselling [17], with an appropriate clinical professional supervising the research, but not explicitly disclosing any results themselves.

There is no international consensus on handling and communicating incidental findings. Contingency plans may be adequate but non-standardised in up to 47% of international research groups [8], or sometimes might be inadequate [30]. Unofficial US contingency guidelines have recently been published [22]. One of the guidelines recommends that incidental findings are initially disclosed to a participant (or, if they lack capacity, a surrogate) who controls the information and decides whom to consult. It recommends that communication is the responsibility of the principal investigator. If they are not a clinician, communication may be designated to a qualified member of the research team, such as a physician experienced in communication — the preferred option amongst neuroimaging volunteers [40]. The disadvantage of this guideline is derived from a whole-body CT screening study in which results were disclosed to the participant rather than the treating physician [4]; a third of lesions “indeterminate, suspicious or highly suggestive of malignancy or life threatening” had not been followed up 5 years later [69]. In contradistinction to this guideline, other evidence suggests that communication by the participant’s treating physician would be appropriate [63] or ideal [70]. The disadvantage of the latter approach is that the participant may have no control of the information that could enter their medical record before they have been consulted, thereby compromising privacy [1].

Another of the US contingency guidelines recommends communicating an incidental finding in a timely manner consistent with the suspected severity. This communication should be verbal with written follow-up drawing on language used in gaining consent [22]. This approach minimises clinical risk to participants, thereby complying with US Federal regulations [1].

Satisfactory procedures for disclosure may be costly and time-consuming. A practical approach for optimising resources for disclosure may be to use a “sliding scale”, where the mode of communicating incidental findings to the volunteer (e.g. written, internet, telephone, group or face-to-face) matches their risk and severity [65].

Discussion

Most of the UK legal and ethical information identified in this review, and the scant information on volunteers’

expectations, is consistent with the principle that research volunteers should be informed of how their research images will be managed, that measures should be in place for identifying and acting on incidental findings and that information should be disclosed to the subject and their responsible physician in a timely, sensitive and appropriate manner. The wide variation in practice and opinion, however, suggests that these regulations and guidelines are interpreted inconsistently. MDA guidelines on radiological reporting and disclosure of all findings in research MRI are not reflected in DoH and NRES guidance for ethics committees specifically on management of research imaging; the degree to which they are implemented is uncertain, and they do not in any event apply to other imaging modalities. The regulations and guidelines are inconsistent, vague or ambiguous in how they refer to incidental findings, and lack detail as to how the different stages in the process should be followed. There is useful additional guidance in domestic and overseas medical literature and law.

Further research and discussion is urgently required to determine optimum practice for identifying incidental findings and the involvement of radiologists in this process, as they are an expensive and limited resource. Reporting of research images by specialist radiologists, with additional images to improve detection of any incidental findings, may be best practice. The effects of incidentally discovered pathology on an individual subject can be complex and far-reaching. UK guidance on what constitutes relevant findings and to whom they should be disclosed is incomplete. European and US guidelines are more explicit in this regard, but are divided on whether the subject or their treating physician should receive this information first. Either way, the best person to disclose an incidental finding is likely to be a clinician, the volunteer’s GP or a research clinician experienced in communicating sensitive medical information.

An approach to good practice derived from this review is given in Appendix E. However, at national and international levels, discourse of research practice for handling incidental findings is needed, with input from clinical and non-clinical researchers and patients’ representatives. In the UK this will allow practical, lawful and ethically defensible national guidelines to be established that can inform NRES advice to ethics committees and set a precedent for other nations.

Summary of this review

- Explicit information on screening for, and handling of, incidental findings must be provided to participants as part of the consent process.
- Practice on screening of research images for incidental findings by radiologists is highly variable. The UK MDA recommends routine radiological reporting of all research MRI and disclosure of incidental findings, but it is unclear how many centres are compliant and these recommendations do not cover other imaging modalities.
- There is no general ethical obligation or law in the UK for incidental findings in volunteers to be disclosed

to the volunteer, unless the volunteer specifically requests disclosure. Such requirements are mandated in European legislation. Volunteers should have the right not to know of any incidental findings, except if this places others at risk.

- Any disclosure to a volunteer is best performed by a medical practitioner experienced in communicating sensitive medical information. Guidance is divided on whether the subject or their GP should receive this information first.
- A discourse of national and international practice is required in the light of existing legal and ethical frameworks to develop robust and practical guidelines for both research centres and ethics committees considering proposals for imaging research.

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Appendix A

Summary of criteria [21, 22] for institutional review board (IRB) approval of radiological research based on US Food and Drug Administration (FDA) regulations [71, 72] and Department of Health and Human Services [73].

- Risks to subjects are minimised.
- Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects and the importance of the knowledge that may reasonably be expected to result.
- Selection of subjects is equitable.
- Informed consent will be sought from each prospective subject or the subject's legally authorised representative.
- Informed consent will be appropriately documented.
- When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
- When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

A caveat is that, according to one author, little guidance on incidental findings can be derived directly from these regulations. "The regulations under which most IRBs operate were established over 25 years ago and have not been substantially altered in the intervening years. The technology available today that creates the opportunity for incidental findings was not conceived of or considered in the crafting of those regulations." [74]

Appendix B

In 2005 one UK neuroimaging research centre provided information about consent to volunteers, which included the following [6]:

- A paragraph stating "there is a chance of less than 1:100 that your MRI scan may show a significant abnormality of which you are unaware. In such circumstances.....you will be referred to the appropriate specialist in consultation with your general practitioner, if that is what you would like. Such early detection has the benefit of starting treatment early but, in a small number of cases, may have implications for future employment and insurance."
- The authors state any significant abnormality is discussed with the clinical director of the unit, who is a consultant neurosurgeon in active clinical practice. The volunteer is informed that there may be an abnormality and a full clinical MRI investigation is arranged if necessary. Volunteers are reassured that no communication will be made with their family doctor unless they so wish. This is to avoid data entering the medical records that might be used at some future date by life insurers and so on.

Appendix C

Data on the frequency of incidental findings by type of abnormality, age, sex and other demographics of the volunteers are limited [3, 36, 75, 76]. However, there is some detailed breakdown of the 2.7–8.8% intracranial findings on MRI neuroimaging [2, 5, 30, 34, 75, 77, 78], the 12.8% body findings on whole-body MRI [3] and the 5–8% extra-colonic findings on CT colonoscopy [4]. In the last

case, for example, extra-colonic malignancy was found in 0.6–1.0%. Systematic epidemiological evidence may be more desirable for producing demographic data (e.g. age and brain tumour prevalence [79, 80]) as the incidence of "incidental" pathology in research volunteers might be higher than in the general population. This is because subjects with symptoms may be more likely to volunteer, viewing participation in research as an opportunity for a "free scan" [6].

Appendix D

Recommended classification of incidental findings by US authors [1]. Note that these recommendations were designed for all volunteers including those undergoing genetic as well as imaging research. The "recommended

Category	Relevant Incidental Findings	Recommended Action
Strong Net Benefit	<ul style="list-style-type: none"> • Information revealing a condition likely to be life-threatening • Information revealing a condition likely to be grave that can be avoided or ameliorated • Genetic information revealing significant risk of a condition likely to be life-threatening • Genetic information that can be used to avoid or ameliorate a condition likely to be grave • Genetic information that can be used in reproductive decision-making: <ol style="list-style-type: none"> (1) to avoid significant risk for offspring of a condition likely to be life-threatening or grave; or (2) to ameliorate a condition likely to be life-threatening or grave 	Disclose to research volunteer as an incidental finding, unless s/he elected not to know
Possible Net Benefit	<ul style="list-style-type: none"> • Information revealing a nonfatal condition that is likely to be grave or serious but that cannot be avoided or ameliorated, when a research volunteer is likely to deem that information important • Genetic information revealing significant risk of a condition likely to be grave or serious, when that risk cannot be modified but a research volunteer is likely to deem that information important • Genetic information that is likely to be deemed important by a research volunteer and can be used in reproductive decision-making: <ol style="list-style-type: none"> (1) to avoid significant risk for offspring of a condition likely to be serious; or (2) to ameliorate a condition likely to be serious 	May disclose to research volunteer as an incidental finding, unless s/he elected not to know

Category	Relevant Incidental Findings	Recommended Action
Unlikely Net Benefit	<ul style="list-style-type: none"> • Information revealing a condition that is not likely to be of serious health or reproductive importance • Information whose likely health or reproductive importance cannot be ascertained 	Do not disclose to research volunteer as an incidental finding

actions” in the table are contingent on other recommendations from these authors — that the research protocol and consent forms anticipate incidental findings and articulate a bespoke plan for handling them (*e.g.* to disclose incidental findings with a strong net benefit, but not to disclose incidental findings with a possible net benefit).

Appendix E

Consent

The written consent of the subject is obtained after information on the study is explained to them by someone with expertise in communicating this information. The information incorporates:

- Possible disadvantages and benefits of taking part including insurance and occupational issues
- What would happen if other conditions were discovered of which he or she was unaware. This includes disclosure of such information to a medical practitioner who will then disclose this to the participant, and the extent of an investigator’s responsibility to provide medical services to the participant. The participant chooses one option for disclosure, which can be changed at any time:
 - (1) No disclosure of any unexpected finding [except in the interests of public safety]
 - (2) Disclosure of unexpected findings judged ‘relevant’ (possible or strong net benefit from disclosure). Or
 - (3) Disclosure of only those incidental findings with a strong net benefit.
- The prevalence of likely incidental findings
- How their confidentiality will be safeguarded during and after the study and the procedures for handling, processing, storage and destruction of their data match the Caldicott principles and/or the Data Protection Act 1998.
- It must be clear if the data are to be retained for use in future studies and whether further ethics committee approval will be sought. The participant has an option to allow re-contact in future studies.

A lay group reviews this information and provides feedback to the investigator.



‘Proactive’ reporting

Routine reporting by expert clinical imager who therefore can determine the ‘relevance’ of unexpected findings and whether there is no, possible or strong net benefit of disclosure to the participant.

Alternatively (and preferably) ‘very proactive’ reporting

Additional images are obtained to optimise this decision making process.



Disclosure

- Timely disclose in accordance with plan articulated during consent
- Disclosure by medical practitioner experienced in communicating sensitive medical information